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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/608,710 | 06/27/2003 | Michael D. Edge | GTC-42D | 6943 |

31904 7590 05/19/2005

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| EXAMINER | |
|---|---|
| WEHBE, ANNE MARIE SABRINA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/608,710 | EDGE ET AL. | |
| | Examiner | Art Unit | |
| | Anne Marie S. Wehbe | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's amendments to the claim and specification, and the response to the previous office action received on 2/9/05 have been entered. Claim 18 is pending the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

### *Nucleic acid and/or Amino acid Sequences*

Applicant's amendments to pages 23 and 39 of the specification places this application in compliance with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures, see 37 CFR 1.821 through 1.825.

### *Claim Rejections - 35 USC § 103*

The rejection of claim 18 under 35 U.S.C. 103(a) as being unpatentable over WO 97/42329, 11/13/97, hereafter referred to as Copley et al., in view of U.S. Patent No. 5,959,171, 9/28/99, filed on 8/17/94, hereafter referred to as Hyttinen et al., is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant rejection for reasons of record as discussed in detail below.

The applicant has amended the claim to add the limitation that the fusion protein is under the control of a milk-specific protein promoter and has an integrated signal sequence related to that of the milk-specific protein promoter. The applicant argues that Copley et al. does not teach this added limitation. In response, the previous office action set forth that Copley et al. teaches the expression of the encoded fusion protein comprising a humanized anti-CEA antibody and human carboxypeptidase B in transgenic non-human mammals in which the nucleic acid encoding the fusion protein is operably linked to a mammary promoter to direct the expression of the protein in the mammal's milk (Copley et al., page 17, lines 1-14). Copley et al. further teaches the recovery of the protein from the milk of the transgenic mammals (Copley et al., page 17, lines 9-10). While Copley et al. generally teaches using mammary specific promoters to direct the expression of the protein in the milk of the transgenic mammal, the rejection of record is not based solely on the teachings of Copley. The rejection of record supplements the teachings of Copley et al. with the teachings of Hyttinen et al. Hyttinen supplements Copley et al. by teaching that expression of fusion proteins in the milk of transgenic mammals was well developed. Hyttinen teaches that the general idea of making and using transgenic bioreactors for the production of large quantities of proteins, particularly human proteins, was suggested as early as 1986 and that numerous examples of transgenic bioreactors exist in the art, citing references from 1991-1992 (Hyttinen et al., column 1). Hyttinen et al. further supplements Copley et al. by providing specific guidance as to the types of mammary specific promoters useful for expressing the fusion proteins in the milk of transgenic mammals. In particular, the applicant is pointed to paragraphs 23 and 24 of Hyttinen et al. which particularly teach to use regulatory elements such as promoters and enhancers from milk protein genes to direct the expression of the fusion

proteins. Hyttinen et al. also specifically teaches that the expression system for the fusion protein contain a signal peptide that is preferably derived from the same milk protein gene as the regulatory sequences (Hyttinen et al., paragraph 24 ). Thus, Hyttinen et al. supplements Copley by providing the specific teachings and motivation to include a milk-specific protein promoter and has an integrated signal sequence related to that of the milk-specific protein promoter in the transgene as recited by the claim as amended. Thus, applicant's argument that Copley et al. does not teach the limitation added by amendment is not persuasive as the requisite teachings for the added limitation are provided by Hyttinen et al.

The applicant further argues that Hyttinen et al. cannot be combined with Copley et al. because Hyttinen et al. teaches away from the current invention. According to the applicant, the current claims focus on transgenic animals that express active enzymes, whereas Hyttinen et al. teaches away from the claimed invention by using transgenic animals to produce inactive molecules. The applicant argues that the Hyttinen et al. reference does not teach or suggest producing a fusion protein which includes an enzyme in active form, since Hyttinen et al. teaches that the expression of enzymes in transgenic bioreactors can cause severe side effects. In response, Hyttinen et al. teaches fusion proteins comprising potent polypeptide such as enzymes which are biologically less active than the free form of the enzyme (Hyttinen et al., column 2, lines 39-42, and columns 3-4). While the fusion proteins described by Hyttinen et al. may not demonstrate 100% of the activity of the free wild type enzyme, a less active enzyme still equates to a "biologically active" enzyme as required by the instant claim as written. The appellants are reminded that claim 18 does not recite any specific level of activity, nor does the specification as filed define the phrase "biologically active form" as meaning that the enzyme present in the form

of a fusion protein has 100% of the enzymatic activity as the enzyme in its free form. The phrase "biologically active form" is very broad and reads on a fusion protein where the enzyme portion has any level of biological activity. Hyttinen et al. clearly teaches that in one embodiment of the invention the fusion protein comprising an enzyme does in fact have biological activity. The applicant is reminded that in determining patentability, claims are to be given their broadest reasonable interpretations, and limitations are not to be read into claims from the specification. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Further, Hyttinen clearly sets forth the purpose of their invention which is to offer a practically applicable alternative to mammalian tissue culture systems for the production of "potent" polypeptides which minimizing potential side effects from the expression of these polypeptides in the mammal by 1) using a mammary gland specific expression system that directs the produced fusion protein into the milk and 2) producing the "potent" polypeptides as fusion proteins. Column 2, lines 50-54, of Hyttinen et al. state, " One object of the present invention is to provide a process for the production and secretion of a **biologically active** polypeptide as a fusion protein into the milk of a mammal without causing to said mammal severe side effects associated with ectopic expression or leakage of said polypeptide" (emphasis added). The working example described by Hyttinen et al. in fact presents a fully successful example of their invention. The transgenic mice described in column 10 of Hyttinen express the beta-lactoglobulin-hEPO fusion protein in their milk at high concentration (0.2-1 mg/ml) and are healthy (Hyttinen et al., column 10, lines 30-38). The fact that one of the mice had a slightly elevated hematocrit, while still considered healthy, simply proves that the fusion protein was in fact biologically active. Thus, a proper evaluation of the complete teachings of Hyttinen et al. as

indicated by *EWP Corp. v. Reliance Universal, Inc.*, *In re Bode*, and *In re Snow*, as cited by the applicants, clearly shows that Hyttinen et al. not only contemplated producing biologically active fusion proteins comprising enzymes, but in fact provided a clear example of the successful production of just such as biologically active protein in milk of a transgenic mouse. Therefore, for the reasons discussed in detail above, applicant's arguments concerning the teachings of Hyttinen et al. have not been found persuasive.

Finally, the applicant argues that neither Hyttinen nor Copley, alone or in combination, teach or suggest the expression levels of the fusion protein in milk as claimed. This is not agreed. The claims recite an expression level of the fusion protein of at least about 0.1 mg/ml in milk. Hyttinen et al. teaches transgenic mice which express the beta-lactoglobulin-hEPO fusion protein in their milk at high concentration of 0.2-1 mg/ml (Hyttinen et al., column 10, lines 30-35). Therefore, in view of the motivation provided by Copley et al. for making a transgenic mammal which expresses a fusion protein comprising carboxypeptidase in the mammal's milk, and in view of the teachings of Hyttinen et al. that fusion proteins can be expressed in the milk of transgenic mammals at concentrations of 0.2-1.0 mg/ml, it would have been *prima facie* obvious to the skilled artisan at the time of filing to make and use the transgenic mammals which secrete carboxypeptidase fusion proteins in the milk as described by Copley et al. to produce at least 0.1 mg/ml of the carboxypeptidase B enzyme fusion protein in the transgenic milk. Further, based on successful use of transgenic bioreactors in expressing large quantities of a variety of human proteins and enzyme containing fusion proteins as taught by Hyttinen et al., and the successful demonstration of the expression of 0.2-1.0 mg/ml of an enzyme fusion protein in transgenic milk by Hyttinen et al., the skilled artisan would have had a reasonable expectation of success in

expressing at least 0.1 mg/ml of carboxypeptidase B enzyme fusion protein in the milk of a transgenic mammal using the transgenic mammals described by Copley et al. Therefore, applicant's argument is not persuasive.

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the**

**new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER